transduction is regulated and compartmentalized in the cilium or flagellum membrane, in the absence of the specialized domains and machinery known to control signaling at the membrane of the rest of the cell (i.e., coated pits, membrane vesicular structures, etc.). In addition, these data have major implications for the understanding of signal transduction in the mammalian cilium. This is an especially important issue in light of recent results demonstrating that PDGF-A, Sonic hedgehog (Shh), and possibly many other pathways require cilia for normal activity (Haycraft et al., 2005; Pazour and Witman, 2003; Schneider et al., 2005). For example, recent reports have revealed that Smoothened, a transmembrane protein involved in the Hedgehog pathway, translocates to the cilia in the presence of Shh and that all three of Hedgehog's Gli-type transcriptional effectors localize to a domain at the tip of the cilium (Corbit et al., 2005; Haycraft et al., 2005; Huangfu and Anderson, 2006). Thus, it has been speculated that the tip of the cilium is a specialized compartment where ligand-induced modifications of the Gli proteins occur in response to Shh. Indeed, loss of cilia is known to inhibit Gli2 activity and processing of Gli3; however, due to the limitations of the mammalian system, it is not yet feasible to evaluate direct involvement of IFT proteins in this process. It is tempting to speculate that, as seen for PKG in *Chlamydomonas*, there is an IFT-dependent recompartmentalization of the Gli proteins (or equivalent proteins in other pathways) in response to ligand that regulates pathway activity. Overall, the data in the Wang et al. (2006) publication will have a major impact on how we perceive the functions of IFT in some of the most critical pathways required for normal development and tissue homeostasis in postnatal life.

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Grasp a pTyr-Peptide by Its SOCS

Signaling via suppressors of cytokine signaling (SOCS) is an important negative feedback system for cytokine-mediated signal transduction. Recently in *Molecular Cell*, Babon et al. (2006) described the tertiary structure of SOCS3 in complex with a phosphotyrosine-containing peptide from the IL-6 receptor subunit gp130, and they identified the specific amino acids that are critical for binding.

Cytokines are secreted glycoproteins that play crucial roles in development, immune responses, hematopoiesis, endocrine function, inflammatory responses, and a variety of diseases. Binding of cytokines to their receptors results in the oligomerization of receptor subunits and activation of the Janus family tyrosine kinases (JAK) constitutively associated with receptors. Subsequent tyrosine phosphorylation of receptor cytoplasmic domains gives rise to the formation of SH2 domain binding sites for a variety of signaling molecules. One of the major signaling molecules in cytokine signaling is the "signal transducers and activators of transcription" (STAT) family of latent transcriptional factors (STAT1-6). STATs recruited to the receptors are then tyrosine phophorylated by JAKs and translocated to the nucleus to induce transcription of target genes (Sehgal et al., 2003) (Figure 1A). Since prolonged and enhanced activation of cytokine signaling causes detrimental biological consequences including autoimmune and inflammatory disease, the pathway must be tightly regulated. One feedback inhibitor induced by STATs is called "suppressor of cytokine signaling" (SOCS).

The SOCS family consists of eight members: SOCS1–SOCS7 and cytokine inducible SH2 protein (CIS) (Alexander and Hilton, 2004; Elliott and Johnston, 2004; Yasukawa et al., 2000). SOCS family members share a common architecture, including a central SH2 domain and a C-terminal SOCS box. In addition, SOCS3 has a 12 residue kinase inhibitory region (KIR) followed by an extended SH2 subdomain (ESS) (Figure 1A). Thus, induced SOCSs inhibit cytokine signaling, although the mode of the inhibition can vary among family members. For example, SOCS1 directly binds to JAK, while SOCS3 uses its SH2 domain to bind phosphorylated tyrosine (pTyr) residues in receptors such as gp130 (Y759), LeptinR (Y985), and EpoR (Y401), just as SOCS2 binds to Y595/Y487 of the growth hormone (GH) receptor.

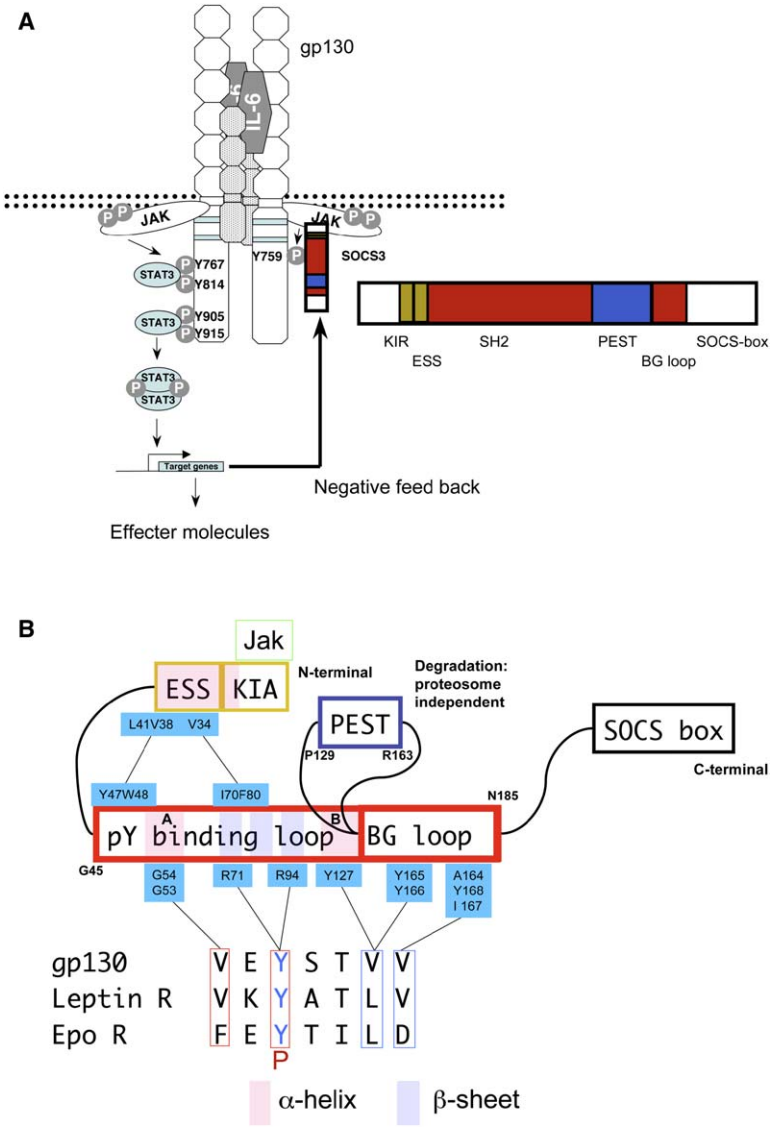

Figure 1. SOCS3 Is a Critical Negative Regulator of IL-6-Mediated Signaling

(A) Y767, Y814, Y905, and Y915 are STAT3 binding pTyr of human gp130. Y759 (or Y757 of mouse gp130) is the SOCS3 binding pTyr. (B) View showing SOCS3 binding the corresponding gp130-derived pTyr-peptide.

Once incorporated into the receptor complex, SOCS3 inhibits JAK kinase activity through its KIR domain. In addition, the SOCS box recruits the ubiquitin-transferase system and thereby functions as an E3 ubiquitin ligase to degrade other signaling molecules associated with SOCS N-terminal regions.

The importance of SOCS-mediated negative feedback has been well established in knockout mice; severe inflammatory disease due to enhanced IFNγ signaling, gigantism due to enhanced GH signaling, and placental defects due to enhanced LIF signaling have been observed in SOCS1$^{-/-}$, SOCS2$^{-/-}$, and SOCS3$^{-/-}$ mice, respectively (Alexander and Hilton, 2004; Elliott and Johnston, 2004). Knockin mice expressing mutant gp130 where the SOCS3 binding site, tyrosine 759, is replaced with phenylalanine (gp130$^{Y759F/Y759F}$ or Y759F or just F759 mice) show enhanced and prolonged activation of STAT3, resulting in spontaneous development of rheumatoid arthritis-like autoimmune joint disease as they age (Atsumi et al., 2002). SOCS3 is a negative regulator of the IL-6 family cytokines, which utilize gp130 as receptor subunit (Figure 1A). The IL-6/gp130/JAK/STAT3 signaling pathway is conserved among vertebrates and invertebrates; in *Drosophila*, the corresponding cytokine, receptor, JAK, and STAT proteins are named Unpaired (Upd), Domeless (Dome), Hopscotch (Hop), and Stat92E, respectively (Hou et al., 2002; Sehgal et al., 2003). Three SOCS-like genes have also been identified in *Drosophila* and are hypothesized to inhibit Stat92E-mediated signaling. The Upd/Dome/Hop/Stat92E pathway plays crucial roles in development, including sex determination, oogenesis, segmentation, and planar cell polarity determination. In zebrafish, STAT3 controls epithelial-mesenchymal transitions (EMT) and cell polarity determination during gastrulation (Miyagi et al., 2004; Yamashita et al., 2002, 2004). Thus, IL-6/gp130/JAK/STAT3 signaling plays crucial roles in the regulation of cell proliferation, differentiation, survival, and movement in response to a variety of cytokines and growth factors in various biological processes including gastrulation, organogenesis, and wound healing, and its dysregulation is involved in a variety of diseases, such as cancer and inflammatory diseases (Sehgal et al., 2003). In this sense, it is crucial to clarify the molecular mechanisms of each component

signaling molecule, such as SOCS3. Extensive mutagenesis studies involving SOCS3 have been done, but until recently, no structural information was available for any member of the SOCS family.

Norton and colleagues have for the first time determined the solution tertiary structure of SOCS3 in complex with a pTyr-containing peptide from gp130 (Babon et al., 2006). They showed that seven amino acid residues of gp130 form a hydrophobic SOCS3 binding motif (Figure 1B), while the SH2 domain that binds it is comprised of SOCS3 residues Gly45–Asn185. This SH2 domain consists of a central β sheet flanked by an α helix on each face, followed by an unstructured PEST insert of 35 residues and then by the hydrophobic BG loop, which directly contacts the gp130 pTyr peptide. The PEST insert is not critical structurally but regulates protein stability, most likely via a proteasome-independent mechanism. The importance of the ESS for SOCS3′s binding to gp130 was previously reported, but the structural basis of this requirement was not known. Norton and colleagues show that the ESS and the C-terminal half of the KIR are packaged into a single 15 residue α helix immediately N-terminal to the SH2 domain. The hydrophobic side of this amphipathic α helix stacks onto the SH2 domain's central β sheet, on the far side of the pTyr binding site. It also makes direct contacts with the pTyr binding loop and contributes to the loop's geometry. This structure suggests that the SH2-ligand interaction may affect the KIR domain's interaction with JAK or vice versa, revealing a basis for understanding how interactions between the SH2 domain and its flanking regions can coordinate binding of target molecules.

The sequence of the pTyr binding loop of the SOCS3 SH2 domain is conserved in almost all species. This may suggest that the pTyr-containing ligands for the SOCS3 SH2 domain might have a conserved structure. It is reported that SOCS3 binds not only gp130 (Y759) but also Leptin receptor (Y985) and EpoR (Y401). In fact, the amino acid residues by which these cytokine receptors bind to SOCS3 are conserved (the −2 and +3 positions relative to the tyrosine are hydrophobic amino acids in three receptors, while the +4 position is hydrophobic in the leptin receptor and in gp130 [Figure 1B]), supporting the idea that the cytokine receptor family ligands of SOCS3 have a conserved structure. The sequence of SOCS proteins (SOCS1–SOCS7) is also conserved from the C-terminal half of the KIR and ESS domain through the SH2 domain, including the pTyr binding loop. Therefore, it is possible that the binding geometry between SOCS family members and their ligands is conserved.

The work of Norton and colleagues thus establishes a structural basis for the artificial design of SOCS inhibitors and other regulators of cytokine signaling. Indeed, by using peptide fragments of SOCS SH2 domains or their phosphotyrosine ligands, we may gain control of a variety of SOCS-regulated signaling pathways relevant to development, immunity, and cancer progression.

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Sister Chromatid Cohesion at the Centromere: Confrontation between Kinases and Phosphatases?

Accurate chromosome segregation in mitosis and meiosis requires that the cohesin complex be protected at the centromere by the Shugoshin/MEI-S332 protein family. Recent studies show that Sgo directly binds the phosphatase PP2A, tethering it to the centromere where it can protect cohesin subunits from phosphorylation, and that localization of Sgo/MEI-S332 itself is regulated by phosphorylation.

Physical attachment, or cohesion, between centromeres of sister chromatids is essential for the two sister